Simmonds' Disease

Report of a Case

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Paulesco in 1907 drew attention to a syndrome which developed in animals following removal of the anterior lobe of the pituitary gland. Acquainted with this experimental work, Simmonds in 1914 was able to correlate ante-mortem and post-mortem findings in a woman who died with undue emaciation and premature ageing, and who at autopsy was found to have destruction of her anterior pituitary. It is obvious that the clinical syndrome was known before these papers of Paulesco and Simmonds appeared, but its relationship to destruction of the anterior pituitary was not recognised until Simmonds wrote his now classical paper and applied Paulesco's experimental work to human medicine.

Silver (1933) has defined the syndrome as "a clinical state, most common in women, characterised by progressive extreme emaciation, premature ageing, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by depression of the basal metabolic rate. Untreated it is a progressively fatal disease, usually terminating suddenly with a short period of coma." While this definition undoubtedly covers many of the cases, it certainly does not apply to them all. As is becoming more generally appreciated, emaciation is not a *sine qua non* for the diagnosis of Simmonds' disease. If we apply a pathological definition to the syndrome, it is likely that the true clinical picture will become much clearer and more cases will be recognised.

Briefly then, Simmonds' disease is better considered as a condition resulting from the destruction, partial or complete, of the anterior lobe of the pituitary gland. The actual cause of the destructive process is of secondary importance to a proper understanding of the condition. As Sheehan (1939) says: "It must therefore be emphasised that the one primary requirement of the syndrome is that there shall have been some gross destructive lesion in the anterior pituitary." The fact that a fairly large amount of anterior pituitary tissue must be lost before recognisable symptoms can occur was first pointed out by Simmonds (1918). The symptoms themselves can involve any system of the body, they are of very varied incidence, and practically any one of them may or may not occur without any satisfactory explanation of its presence or absence. Furthermore, they do not show any regularity of association (Sheehan, 1939).

The following is a report of a case of Simmonds' disease in a male, verified at post-mortem examination, and in whom emaciation was notable for its absence, despite the fact that the patient had had the condition for at least six, and possibly sixteen, years.

Report of Case

The patient was a male aged 48 years. He was married and had two children, one born in 1925, the other in 1927. His wife and both children are alive and quite

normal in every way : they have not suffered from any serious or significant illness. The patient's blood relatives did not suffer from any mental or endocrine abnormality.

In 1931 the patient, according to his wife's story, disappeared from home for a period of five months. Up to that time he had led a perfectly normal life. He had been employed as a night watchman. His wife has stated that up to that time too their sexual relationships had been quite normal.

In December, 1931, he was admitted to the Belfast City Hospital with a mild infection of his conjunctivæ. His wife was notified, and on his discharge within a few days he went back to live with her. His behaviour was not, however, normal; he had definite persecutory ideas and thought that his wife and one of his children were trying to kill him. His mental condition deteriorated rapidly, and he was admitted to the Belfast Mental Hospital in April, 1932. He was described then as being a rather small but well nourished man; he was certainly not obese. His hair was dark and he had a normal male distribution of body hair. On his head he had a thick crop of dark hair. His expression was "depressed," but otherwise there was no abnormality in his appearance. On physical examination all systems were found to be normal. He said that he had stopped work nine months previously because of his "nerves." He was dull and quiet and did not talk freely. He thought he was being followed everywhere, his food was being poisoned, and that he had some "dirty and bad" disease. He blamed all this on his wife and one of his children. He attributed his immediate breakdown in mental health to the loneliness of his work as a night watchman.

During the next seven years he remained in the Mental Hospital. At times he was dull and stupid, at other times he was restless and excited. His mental condition did not improve in any way; if anything, he seemed to deteriorate. His physical condition remained, however, good until March, 1939, when he had a severe attack of bronchopneumonia. With the onset of this acute illness he became quite mute. Within two months he had completely recovered from this physical illness but was still mute. He was very dull and resistive. He then developed a conjunctivitis and a furunculosis of his pinna. He recovered from this within a few days and apparently had no complications, intracranially or otherwise : at any rate there is no evidence that he had any more serious trouble. Six months later his mental condition had improved considerably. He was still mute, but he was described at this time as "bright and active, working industriously, and always clean and tidy." Some time later, in October, 1941, he had become sufficiently improved to be discharged from hospital under the care of his wife and sister.

On discharge from hospital his wife stated that apart from being rather pale and very thin he looked quite normal. He had a normal distribution of body hair and he had not started to lose his scalp hair. He was rather quiet and dull. He expressed no desire to lead any kind of sex life again.

Within a year his whole appearance had noticeably changed. He no longer had to shave once a day but found that once a week was sufficient. And, as his wife

said, "It was vanity which made him shave as often as that!" He began to get fat and to lose his scalp hair. He often had headache, and very frequently vomited in the mornings. He was unable to do any kind of work, being very easily tired and always lethargic. He did not like cold weather; in fact, he apparently always wore a heavy overcoat, even on the warmest day in summer. He was said to turn a yellow or green colour at times; this lasted a few hours, then his usual pallor returned. This green colour must have been very noticeable, since some of his neighbours volunteered the information when they were asked to recall and describe the appearance of the patient.

More or less in this state, he existed until his final illness. On 9th March, 1947, he was admitted to the Belfast City Hospital in coma. On examination he was found to be a "stout man of medium height." He had very little scalp or body hair. He was very pale and his skin was dry and cold. His pulse was not palpable and his heart sounds very faint. His respiratory and alimentary systems were normal on examination and his tongue was dry and clean. His pupils were found to be equal, central and dilated; they did not react to light. All deep reflexes were absent and his limbs were quite flaccid.

He died within a few hours and before any other investigations or a more complete examination could be carried out.

Post-Mortem Examination

The following were the essential findings of the post-mortem examination. Negative findings, except where significant, are omitted.

The body was that of a rather short, "plumpish" man, who looked rather older than his forty-eight years. He was extremely pale. There was complete lack of body hair and almost complete lack of scalp hair. His skin was dry and rather coarse. There was some œdema of his ankles. Neither testicle was in the scrotum. As found later, the left one was absent or replaced by a small amount of unrecognised fibrous tissue and the right testicle was in the inguinal canal.

Body Cavities.—All contained a moderate amount of œdema fluid. There were dense adhesions in the pleural cavities.

Heart.—This was rather small in size, weighing 270 grm., but there was some hypertrophy of the musculature of the right ventricle (6 mm. thick). The left ventricle was 1 cm. thick. On histological examination there was marked vacuolation of individual muscle cells and considerable œdema of the myocardium. In view of this it may be concluded that the heart was actually very much reduced in size, in spite of the hypertrophy of the right side.

Lungs.—The pleura showed evidence of previous inflammation, being thickened and fibrotic. There was considerable emphysema confirmed on histological examination. There was also some cubical metaplasia of alveolar walls and squamous metaplasia of the lining epithelium of the bronchi. There was some œdema of the bases of the lungs.

Liver.—This viscus was only slightly reduced in size, weighing 1,260 grm. The

hepatic cells showed vacuolation of their cytoplasm. There was a marked degree of brown atrophy around the portal tracts.

Spleen.—This was very small, weighing only 110 grm., yet histologically there was marked congestion of the splenic pulp.

Kidneys.—These were somewhat reduced in weight, being about 100 grm. each. Histologically there was a marked degree of vacuolation of the cells of the tubules, especially of the lower parts of the nephron. Over all, one had the impression of atrophy of the organ.

Pancreas.—Again there was no very definite abnormality, only an impression of general atrophy.

Adrenals.—Both glands were rather small. On microscopic examination the capsule was found thickened with fibrous tissue. The cortex was markedly reduced in size, being about one-third of the normal minimal width. The zona glomerulosa was only slightly narrower than normal, but the cells of this layer contained a large amount of lipoid material. The zona fasiculata was noticeably reduced in width, but the zona reticularis was almost entirely, and in places completely, absent.

Thyroid.—All acini were rather small, and there was a very definite atrophy of the gland. There was no marked lymphocytic infiltration, a finding which has been described in many cases of Simmonds' disease.

Bone Marrow.—A specimen of bone marrow from the vertebral column showed abnormal but incomplete fatty replacement of the marrow. Again the picture of atrophy was apparent.

Testes.—The spermatogenic tissue has been completely replaced by a very homogenous hyaline type of tissue, and no normal sperm-producing cells were seen. Of great interest was the absence of the interstitial cells of Leydig. In other words, complete atrophy of the whole of the testis was present. This finding was of special interest, in view of the fact that in 1925 and 1927 the patient apparently became the father of two children. The fact that the left testicle was absent and the right incompletely descended must be taken as coincidental, and the extensive atrophy of both the spermatogenic and endocrinal cells of the right gland be assumed to be due to deficiency of anterior pituitary secretions.

Pituitary.—At post-mortem the gland was noticed to be very small. The posterior clinoid processes extended abnormally far forward as though "collapsed" over the shrunken gland. On microscopical examination the anterior lobe was found to be almost completely replaced by fibrous tissue. Serial sections of the gland were made in the search for more anterior lobe cells, but no more were found. Those few which remained were, for the most part, chromophobe cells. In one area a small nest of lymphocytes was detected, but nothing to indicate a possible etiological factor. Evidence of tuberculous or syphilitic destruction of the gland was searched for in vain. The posterior lobe, on the contrary, remained almost completely intact, apart from a certain fibrous tissue encirclement with patchy fibrosis of its anterior margin. This, of course, is also against a destruction by any form of granulomatous tissue.

This selective destruction of anterior lobe would seem to indicate a vascular etiology akin to the end result of the post-partum destruction, so important in females. However, the etiological agent in this particular case remains obscure.

Brain.—There was evidence of some degree of cerebral œdema, with flattening of the convolutions and slight cerebellar coning. A section through the hypothalmus showed a little subependymal gliosis. There was a fairly definite dropping out of cells in the nucleus supraopticus and a well marked pallidal siderosis.

Aorta.—There was a moderate degree of atheromatous degeneration, but no other lesion noted. There was no evidence of syphilis.

Skin.—A section of skin from the abdominal wall showed a definite atrophy and replacement by adipose tissue of some of the sweat glands, a finding which is in keeping with the clinical condition of the skin.

Summary

Simmonds' disease.
Fibrosis of anterior lobe of pituitary.
Atrophy of all viscera (microsplanchnia).
Cryptorchidism and hypogonadism.
Pulmonary emphysema and right heart hypertrophy.
The immediate cause of death was probably a severe attack of hypoglycæmia.

Commentary

It will be seen, therefore, that although the fundamental finding of anterior pituitary destruction was present in this case, and that therefore the case was one of Simmonds' disease, emaciation was absent. However, the case fits into the so-called "pituitary myxœdema, or Simmonds' disease masquerading as myxœdema" (Means *et al,* 1940). The fact that emaciation is not found in all cases of Simmonds' disease was, apparently, first pointed out by Sheehan (1939). He wrote: "This type of Simmonds' disease is relatively common, but the cases frequently remain undiagnosed . . . The confusion appears to rise from the misconception that patients with Simmonds' disease usually show cachexia."

There are four main types of Simmonds' disease (Sheehan, 1939; Cameron, 1945).

1. *The typical post-partum case of Simmonds' disease.*—Here there is absence of lactation and sometimes hypoglycæmia following a complicated delivery usually in a multipara. The uterus becomes superinvoluted and the external genitalia atrophic. Menstruation fails to return and libido is absent. There is a gradual loss of body hair. Mental apathy and extreme sensitivity to cold develop. The patient may look myxœdematous or prematurely senile. The weight is usually little altered unless there is great anorexia. The blood pressure is low. The basal metabolic rate is about 25 per cent. There is a hypochromic anæmia sometimes with a definite eosinophil leucocytosis similar to that occasionally seen in myxœdema. The blood cholesterol may be a little raised and the blood sugar rather low. After ten, twenty, or thirty years the patient may become typically myxœdematous or may develop

mental changes with anorexia and some loss of weight. At this stage the anæmia may become hyperchromic, the basal metabolic rate may fall to 35 per cent, but the blood pressure is usually normal. Finally the patient goes into coma and dies usually as a result of hypoglycæmia.

It will be seen that this description of Simmonds' disease given by Sheehan (1939) and representing "the typical post-partum case" differs in a great many respects from the generally imagined clinical picture of the condition.

2. *Pituitary Myxœdema.*—Here the patient exhibits typical myxœdema. A differential diagnosis from primary thyroid insufficiency is of great importance, because administration of thyroid in the usual dosage may precipate acute failure of the adrenal cortex, and death result. There are now quite a number of reports in the literature of such cases. A case was described in detail by Castleman and Hertz (1939). Their patient was a woman of 48 years. She was said to be moderately obese, and this obesity was of no special type, being fairly generalised. The onset of her ill health was ten years previously following pregnancy. The authors noted as a striking feature "the preservation of such excellent nutrition despite chronic failing health over a period of ten years." This case was diagnosed clinically as one of myxœdema. She was given thyroid, and, as the authors state, "It was . . . quite likely that our patient died of adrenal insufficiency after the attempt to relieve her thyroid deficiency." It would appear as if the deficiency of thyroid hormone compensates to some extent for the deficiency of adrenal secretions. The whole organism is made to work at a lower speed. Any attempt to increase the rate of working of the organism, by administering a single hormone such as thyroid, makes manifest a gross deficiency of other hormones. Castleman and Hertz suggest that a differential diagnosis may be made if the possibility is always borne in mind in cases of myxœdema in which earmarks of other endocrine deficiencies are present, such as onset of early amenorrhœa (instead of the more usual metrorrhagia), or signs or symptoms of adrenal insufficiency. To this might be added radiography of the pituitary fossa for signs of destruction to the clinoid processes or abnormal calcification in a tumour, etc., and other signs of a pituitary tumour should also, of course, be sought. Castleman and Hertz were able to find six other similar cases in the literature, and Biggart (1941) reported two cases which presented as myxœdema and were found at post-mortem to be examples of Simmonds' disease.

3. *Pituitary Addison's Disease.*—This is a most interesting sub-group of Simmonds' disease. The name is applied to those cases which show predominantly the asthenia typical of destruction of the adrenal cortex. They may show all the symptoms and signs of Addison's disease with one important exception, namely Addisonian pigmentation, which is rarely seen (Sheehan, 1939). Of course, in this respect, the presence of other endocrine abnormalities may point to the correct diagnosis. A typical case has been reported by Moss (1942).

4. *Mild Simmonds' Disease.*—Since all grades of damage to the pituitary are possible, all grades of severity of clinical symptoms should be possible. Sheehan states that in these cases there is nearly always a pronounced, and often a complete,

recovery if patients with a small post-partum necrosis become pregnant again. However, it must be pointed out that conditions which have led to the complicated delivery in the first instance are liable to recur on a subsequent occasion with disastrous results. The improvement in the patient's condition is attributed to the physiological hypertrophy of the remaining pituitary tissue which normally occurs during pregnancy, but in these circumstances subsequent regression to the previous (reduced) volume does not occur.

Mental Symptoms.—The interpretation of the mental changes found in Simmonds' disease is not at all straightforward. This aspect of the condition has been reviewed by Wadsworth and McKeon (1941). They state that there does not appear to be a uniform mental symptomatology. They attribute apathy, somnolence, depression, and slowing of mental processes to the pituitary disease itself, and state that transient attacks of excited, restless behaviour accompanied by delusions or vivid hallucinations are very likely due to states of severe hypoglycæmia. It would appear that these abnormal states can be dramatically relieved by intravenous administration of dextrose. A case was reported by these authors which showed manic-depressive psychosis with associated Simmonds' disease due to post-partum necrosis of the pituitary. In view of the fact that the patient gave a history of two rather vague periods of depression, one following the death of her father and the other the death of her mother, Wadsworth and McKeon were inclined to regard this previous history as indicative that the mental abnormality in their patient was not due to pituitary destruction. Nevertheless, it was only after the complicated delivery that really severe mental symptoms ensued, and the fact that anyone should feel depressed following the death of their parents, especially since no other periods of depression were noted prior to the occurrence of the organic lesion in the pituitary gland, is surely not enough evidence on which to make a diagnosis of double pathology.

In the discussion on this aspect of their case these authors noted that Grinker (1939) had pointed out that the symptom complex in manic-depressive psychosis is identical with the variations of mood accompanying hypothalmic lesions. Electrical stimulation of the anterior hypothalamus produces restlessness, excitement, euphoria, and mania; stimulation of the posterior portion causes sleepiness and unconsciousness. Against this hypothesis in the fact that, with present histological technique, no constant organic lesion has been found in straightforward cases of manic-depressive psychosis occurring in man. Wadsworth and McKeon's case showed histological damage to the hypothalamus. They found degenerative changes in the supraoptic and paraventricular nuclei, which they considered were secondary to the pathological changes in the anterior lobe of the pituitary. They also found in the brain multiple petechial hæmorrhages and some subependymal gliosis, which they thought might be due to hypoglycæmia. As remarked previously, they concluded that they were dealing with double pathology. Nevertheless, the findings in our case are so similar (an illness like manic-depressive psychosis which in our case antedates the physical changes of Simmonds' disease, associated with the pathological changes of sclerosis of anterior pituitary with degenerative changes in the

nucleus supraopticus) to those of Wadsworth and McKeon, that one wonders whether or not the mental changes in our case were the first outward signs of the destructive process which had occurred in the base of the skull and which finally ended in such gross physical abnormalities. If this opinion is not acceptable then, like Wadsworth and McKeon, one must conclude that our patient had two pathological lesions, both of an exactly similar type to their case.

Mental changes occur in about 50 per cent. of all cases of Simmonds' disease, and they are often of the manic-depressive type. In view of this it is difficult not to accept the idea that in our patient mental symptoms preceded physical signs by a period of about ten years.

Admittedly this possibility would be a completely new idea in the symptomatology of the condition and difficult for many people to accept. But since this type of insanity does seem to be related to the hypothalamus, since hypothalmic changes were found in these patients and since the hypothalamus and pituitary gland are so intimately related anatomically and physiologically, the possibility of this organic basis for the mental symptoms cannot easily be excluded.

Etiology.—In an extensive review of the literature, Calder (1932) noted that almost half the cases described had shown as an essential finding a destruction of glandular elements with replacement by scar tissue—"the almost universal result of healed injury." Obviously many pathological processes are capable of bringing about destruction of the pituitary gland. In our case we found only the non-specific scar tissue of any healed injury. The fact that it was limited to the anterior lobe would seem to implicate the vascular system. Perhaps it was a thrombosis or an embolus, perhaps infected, perhaps not. To speculate further regarding the etiological agent which was at work in our patient many years ago, would be futile.

Even the exact mechanism at work in post-partum necrosis is by no means clear. Sheehan (1937) concluded that the lesion is the result of the effects of shock due to hæmorrhage. Most of his cases had a labour complicated by retained placenta, and he postulated that the resulting low pressure allows thrombosis to occur in the engorged sinusoids of the pregnancy gland. Biggart (1941) is not convinced that the mechanism is so straightforward. Many patients die within a week after loss of blood and degrees of shock quite comparable in their severity to those seen in complicated deliveries, yet necrosis of the pituitary has not been seen in such patients. It may be noted too, that even in severe shock an attempt is made to maintain the blood supply to the vital centres, and it would seem that the pituitary would benefit from its juxtaposition to the central nervous system. If the blood supply is so poor as to permit intravascular clotting, this is therefore most likely to occur in other organs. Biggart pointed out that perhaps the placenta may play a more important role than had so far been assigned to it. Large doses of hormones can produce necrosis experimentally in animals, and it is possible that pituitary necrosis may have an endocrine origin. The retained placenta, once the fœtus has become separated, may discharge the contained hormones into the circulation, and these in turn may act upon the anterior pituitary. Such an explanation certainly allows us to understand more easily the limitation of the complication to pregnancy.

Whatever our ideas on the mechanism at work, it is clear that more investigation is required before the condition is fully understood.

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REVIEW

INTRODUCTION TO CLINICAL NEUROLOGY. By Gordon Holmes, M.D., F.R.S. Edinburgh: E. & S. Livingstone Ltd., 1946. 12s. 6d.

It is fortunate for those interested in clinical neurology that Dr. Gordon Holmes has published in book form what he has taught for many years at the National Hospital.

Dr. Holmes' name is a household word with all neurologists, but especially those who have heard him teach or discuss cases. He writes with the same clarity and criticism as he teaches and he very often stimulates the pupil's mind to probe neurological conditions still further and from other angles. This book is not one descriptive of disease, its diagnosis and treatment, so much as symptomatology and its interpretation. Subjects are dealt with rather than diseases. For example, there is a chapter on "Muscle Tone and Co-ordination of Movement." There is one on "Examination of Sensation." A third is entitled "Reflexes," and so on. Diseases affecting the central nervous system are, of course, not forgotten. There is an excellent chapter devoted to "Convulsions and Other Involuntary Movements," while through each chapter clinical conditions are being constantly mentioned to illustrate the subject being discussed.

Pathology is not attempted, except in a short chapter, which shows the ways in which the central nervous system generally may be affected.

Mention must be made of the diagrams, which are original and clear and are a great help to the student.

The book is intended to be an "introduction," but with such a wealth of material available in such a small space, this book will be read and re-read by teacher and student alike. H. H. S.

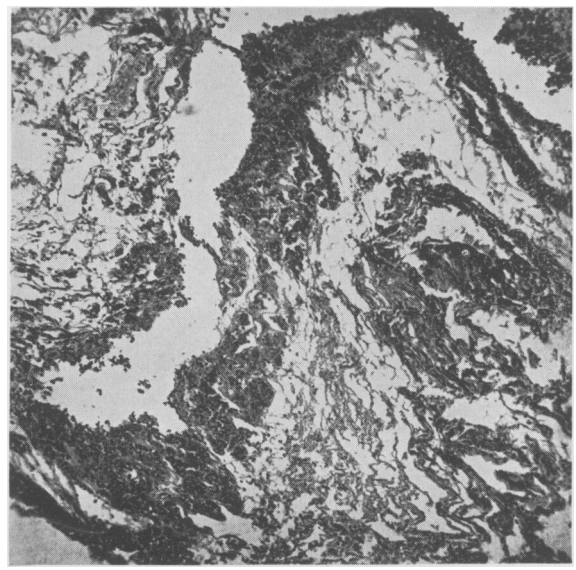

Plate 1 (x60)—Pituitary

Section through anterior lobe to show almost complete replacement by fibrous tissue. Only a few chromophobe cells remain. No eosinophil or basophil cells were detected.

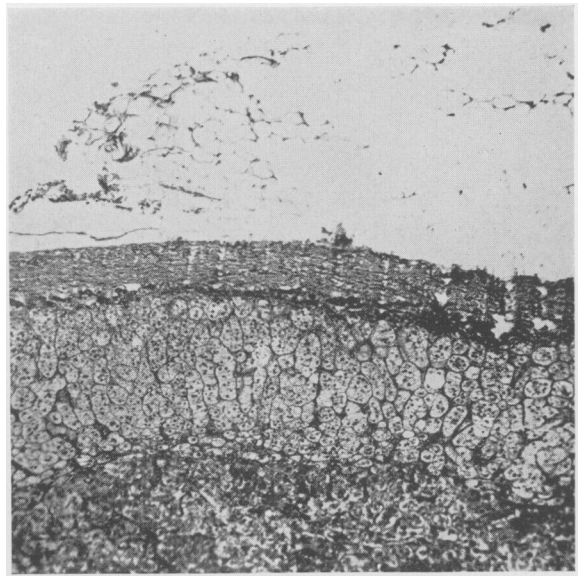

Plate 2 (x60)—Adrenal

Section through cortex to show reduction in width owing to almost complete absence of zona reticularis and great diminution in zona fasiculata. The cells of the zona glomerulosa contain an excess amount of lipoid material. The capsule of the gland is markedly thickened.

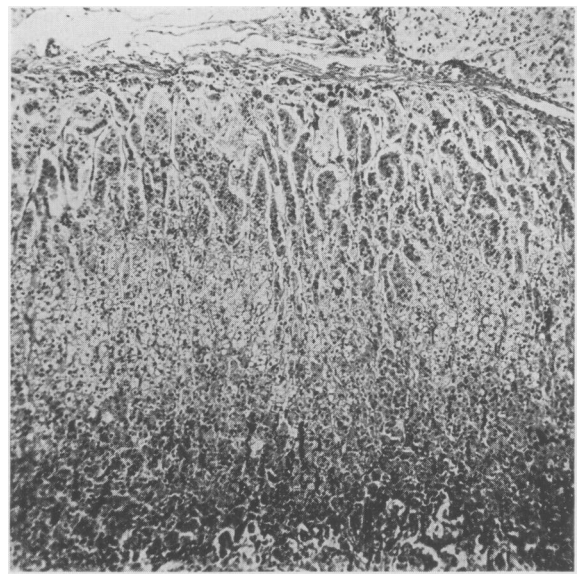

Plate 3 (x60)—Normal Adrenal

Section photographed at same magnification as Plate 2 for comparison.

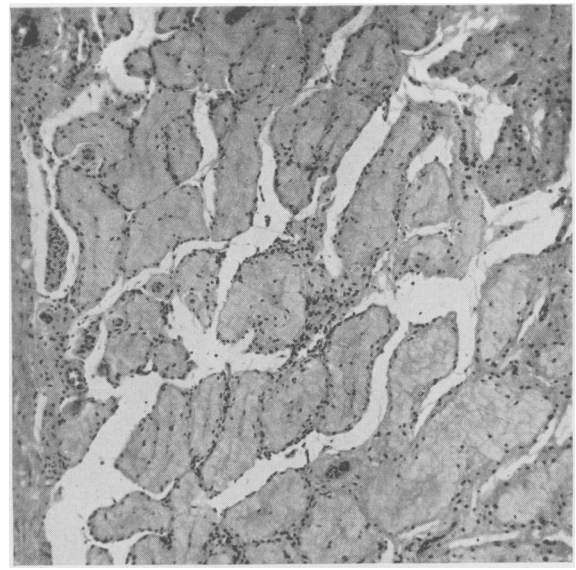

Plate 4 (x60)—Testis

Showing marked atrophy of spermatogenic tissue and replacement by a hyaline type of tissue. Note also absence of interstitial cells of Leydig.

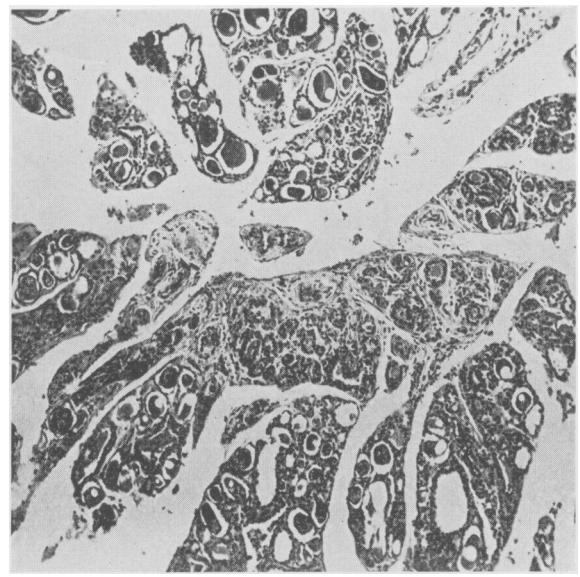

Plate 5 (x70)—Thyroid

Section to show the very marked atrophy of the gland.